UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/042,229	01/11/2002	Shuichi Furuya	087147-0468	5252

22428 7590 10/30/2003

FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	

ART UNIT	PAPER NUMBER
1624	9

DATE MAILED: 10/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/042,229	FURUYA ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-21,30,38 and 40-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-21,30,38,40-42,44-48 and 50* is/are rejected.

7)☒ Claim(s) *43 and 49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' response, which included amendment to claims 2, 13-15, addition of new claims 45-50 and cancellation of claims 4, 22, filed on 8/18/2003, is made of record. Claims 1-2, 6-21, 30, 38 and 40-50 are now pending.

In view of applicants' response, the following apply.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38, 40-42, and 45-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preventing pregnancy and treating prostate cancer, does not reasonably provide enablement for all or any sex-hormone related conditions including those yet to be discovered embraced in the claim language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Following reasons apply.

The instant claims are drawn to "antagonizing gonadotropin-releasing hormone ". Note mode of action of the compound(s) is related to treating diseases as recited in the specification. The scope of the claims includes not only any or all conditions but also those condition yet to be discovered for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various diseases, which is not adequately enabled solely based on the gonadotropin-releasing hormone receptor antagonist binding activity of the compounds provided in the specification at pages 25-

30. The instant compounds are disclosed to have gonadotropin-releasing hormone receptor antagonist activity and it is recited that the instant compounds are therefore useful in treating any or all diseases /disorders, for which applicants provide no competent evidence. In addition, applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the gonadotropin-releasing hormone receptor antagonist activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Huirne, JA, and Lambalk, GB., (Lancet 358(9295): 1793-1803, 2001, PubMed Abstract provided), which suggest that current status at best exploratory and need further experimentation. Note method of use for assisted reproduction and treating prostate cancer is also taught therein.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors

include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating diseases that require antagonizing gonadotropin-releasing hormone activity.

2) The state of the prior art: A very recent publication expressed that the antagonizing gonadotropin-releasing hormone receptor effects are unpredictable and are still exploratory.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for r treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of gonadotropin-releasing hormone receptor antagonist are unpredictable and at best limited to prevention of pregnancy and treating prostate cancer.

6) The breadth of the claims: The instant claims embrace any or all condition including those yet to be related to antagonizing gonadotropin- releasing hormone activity.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of receptor-ligand interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Claims 40-42,44, and 46-48, although positively recite specific condition/disease, examiner could not find prior art support for these conditions/diseases. Applicants may cite references to support the nexus between gonadotropin-releasing hormone receptor antagonist effects and the positively recited conditions/diseases of claims 40-42, 44, and 46-48 to obviate the rejection of these claims.

Claims 1, 2, 6-21 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating prostate cancer and preventing pregnancy for imidazopyrimidine compounds shown in Table 1-4 on pages 79-85 of specification of, does not reasonably provide the same enablement for large

genus of pyrrolopyrimidine compounds with various variable groups generically embraced in the definition of R^1- R^7. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Representative examples of structurally diverse compounds generically embraced in the invention are not shown to possess in vitro activity much less in vivo uses claimed herein. Instant genus of imidazopyrimidine compounds embrace compounds with substituents bearing plethora of structural cores and functional groups and other groups permitted at instant R^1- R^7 variables which include variously substituted monocyclic rings, bicyclic rings, tricyclic rings with variable ring sizes and variable heteroatoms variety of reactive functional groups such COOH, OH ,SH, amido, sulfoxides, sulfones nitrile, carbamates etc. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same bioactivity profile since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for Markush group. Also see MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive art such as the pharmaceuticals.

Note Ex parte Gelles 22 USPQ 2nd 1318, especially the following quote: " The evidence relied upon also should be reasonably commensurate in scope with the subject matter claimed and illustrate the claimed subject matter " as a class" relative to prior art subject matter."

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method of use. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of receptor-ligand interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 6-13,and 16-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ikesu et al US 5,208,141 for reasons of record. To repeat:

Ikesu et al. teach several 5,6-fused heterocyclic compounds, which include compounds claimed herein, for the use as color photographic light -sensitive material. See formula I on col.1 and note the definition of R1, R2, R3, R4, R5, R6, Xa, Xb, Xc, and Y. Also see formulae shown col. 4-6. See the list of compounds shown on col. 7-62. Note Ikesu et al. teach the process of making these compounds on col. 63-65.

Claims 1-2, 6-13, and 16-21 require that D of the five-membered ring bearing bicyclopyrimidine to be a carbon. But Ikesu et al. exemplifies only compounds bearing a ring nitrogen in the five-membered ring of the bicyclopyrimidine compound.

However, Ikesu et al. teach the equivalency of said nitrogen bearing five-membered ring with those not having nitrogen in the ring in the definition of Xa, Xb, Xc, as seen in col. 1-2. Also Ikesu et al teaches Y as hydrogen or a substituent.

Thus one having ordinary skill in the art at the time of the invention was made would have been motivated to make variously substituted bicyclopyrimidinone compounds as permitted by the reference and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above. Note all

disclosures of the prior art including the unpreferred embodiments must also be considered in determining obviousness. See In re Bruckel, 201 USPQ 67.

This rejection is same as made in the previous office action except for the exclusion of cancelled claims 4 and 22.

Applicants' traversal to overcome this rejection is not persuasive.

1. Contrary to applicants' urging, Ikesu et al., clearly teaches equivalency of the core taught with those generically claimed. Thus one trained in the art would be motivated to make the pyrrolopyrimidine core based on the teachings of imidazopyrimidine.
2. As for applicants' traversal that the utility taught is not same as instant utility, it need hot be same. One trained in the art would be motivated to make compounds taught by Ikesu et al. for the utility taught in that reference.

Hence the rejection is proper and is maintained.

Claims 1-2, 6-9,17-21 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abdalla et al. J. Heterocyclic Chemistry 24(2), 297-301, 1987 for reasons of record. To repeat:

Abdalla et al. teaches several 8-cyano-1,4-dihydro-4-oxopyrrolo[1,2-a]pyrimidine-3-carboxylic acids useful as antimicrobial agents. See entire document especially page 297 for synthetic scheme, page 298 for compounds made.

Instant claims recite D as carbon atom and specification shows no compounds with substituted carbon. Hence, D is therefore interpreted as CH or CH_2 group.

While said compound doesn't anticipate the scope of instant claims, they are very closely related, being positional isomers of compound of formula I. Note the when D =CH and R^4 =CN, the instant compound is an positional isomer of compound XVII wherein the 6-positon has hydrogen and 8- position a CN group i.e. 6-cyano of instant compound is a positional isomer of 8-cyano of the reference. However, positional isomers are not deemed patentably distinct absent evidence of superior or unexpected properties. See In re Crounse, 150 USPQ 554; In re Norris 84 USPQ 458; In re Finely 81 USPQ 383 and 387; Ex parte Engelhardt, 208 USPQ 343; Ex parte Henkel, 130 USPQ 474, regarding positional isomers.

Thus it would have been obvious to one skilled in the art at the time of the invention was made to expect instant compounds to possess the utility taught by the applied art in view of the close structural similarity outlined above.

This rejection is same as made in the previous office action except for the exclusion of cancelled claims 4 and 22.

Again applicants' traversal is not persuasive. The instant compound is a optional isomer of the compound taught by Abdalla et al. Applicants have not shown why it is not obvious and why one would not be motivated to make the positional isomer for the utility taught in the reference.

Again, utility taught in the reference needed not be same to make an 103 obviousness-type rejection. One trained in the art would be motivated to make positional isomers for the same utility taught in the reference.

Hence the rejection is proper and is maintained.

Allowabl Subj ct Matter

Claims 43 and 49 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Said claims would be allowed since the specific method of use embraced in these claims are not taught or suggested by the art of record or from a search in the relevant art area.

This action is not made Final.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (703) 305-1674. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (703) 308-4716.

The fax phone number for the organization where this application or proceeding is assigned (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

V. Balasubramanian
Venkataraman Balasubramanian

10/28/2003